19 Polman CH, O'Connor PW, Havrdova E *et al.* A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. *N Engl J Med* 2006;354:899–910.

20 Yousry TA, Major EO, Ryschkewitsch C *et al.* Evaluation of patients treated with natalizumab for progressive multifocal leukoencephalopathy. *N Engl J Med* 2006; 354:924–33.

21 Vincenti F, Kirkman R, Light S *et al.* Interleukin-2-receptor blockade with daclizumab to prevent acute rejection in renal transplantation. Daclizumab Triple Therapy Study Group. *N Engl J Med* 1998; 338:161–5.

22 Beniaminovitz A, Itescu S, Lietz K *et al.* Prevention of rejection in cardiac transplantation by blockade of the interleukin-2-receptor with a monoclonal antibody. *N Engl J Med* 2000;342:613–9.

23 Vincenti F, Larsen C, Durrbach A *et al.* Costimulation blockade with belatacept in renal transplantation. *N Engl J Med* 2005; 353:770–81.

24 Slamon DJ, Leyland-Jones B, Shak S *et al.* Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med* 2001;344:783–92.

25 Use of a monoclonal antibody directed against the platelet glycoprotein IIb/IIIa receptor in high-risk coronary angioplasty. The EPIC Investigation. *N Engl J Med* 1994; 330:956–61.

26 Milgrom H, Fick RB Jr, Su JQ *et al.* Treatment of allergic asthma with monoclonal anti-IgE antibody. rhuMAb-E25 Study Group. *N Engl J Med* 1999;341: 1966–73.

27 Griffiths I, Silman A, Symmons D, Scott DG. BSR Biologics Registry. *Rheumatology (Oxford)* 2004;43:1463–4.

Therapeutic apheresis – plasmapheresis

Khaled El-Ghariani MA MRCP(UK) MRCPath, Consultant Haematologist, *National Blood Service, Sheffield Centre*

David J Unsworth PhD FRCP(UK) FRCPath, Consultant Immunologist, *North Bristol NHS Trust, Bristol*

Clin Med 2006;6:343–7

Background

Apheresis is derived from the Greek, meaning 'withdrawal'. Blood components can be separated by either filtration or centrifugation (Fig 1). Filtration systems allow plasma removal (plasmapheresis) with retention of blood cells. Centrifugal systems are more versatile, allowing plasmapheresis or selective removal of cell types (eg plateletphoresis). Blood components (eg HLA-matched platelets or bone marrow derived 'stem cells') can be 'withdrawn' from healthy volunteers for patient treatment. This article focuses on the removal of pathogenic/abnormal blood constituents.

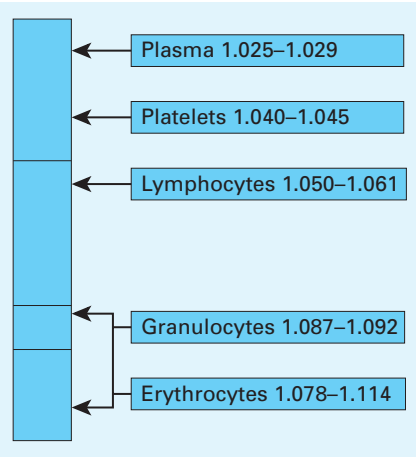

Fig 1. Blood components, separated by centrifugation according to relative density.

Typically, plasmapheresis is an emergency intervention, effective for only a few days unless parallel treatment for the underlying condition is instituted. Plasmapheresis buys time whilst immunosuppression takes effect. Where possible, the patient travels to the treatment centre, but the staff and machine may need to travel to the bedside for sick patients.

Continuous versus intermittent flow apheresis machines

Continuous flow separators (Fig 2) retain healthy blood components and separate plasma for disposal. Using a double-needle kit, blood enters one limb and returns post-centrifugation and plasma removal via another. Continuous fluid replacement maintains isovolaemic balance. The extracorporeal circuit volume is minimal (<150 mol), but none the less large for babies and small infants.

Key Points

Plasma removal (plasmapheresis) directly removes pathogenic autoantibodies and other plasma factors (eg cytokines) to provide temporary therapeutic benefit

Relapse is likely without concurrent immunosuppression and/or other appropriate treatment of the underlying condition (preventing autoantibody production)

Plasmapheresis is a limited resource, largely limited to regional centres; it requires staff experienced in use of specialist apheresis machines

Alternative treatments should be used first (eg Guillain–Barré syndrome for which intravenous immunoglobulin therapy is equally effective)

Commoner side effects relate to central-line insertion, loss of plasma clotting factors and hypocalcaemia caused by citrate anticoagulation

KEY WORDS: autoantibody, immunosuppression, plasmapheresis, vasculitis

In contrast, intermittent flow machines use a single lumen line. Blood enters a spinning centrifuge and separates the plasma. Blood cells are returned to the patient at intervals by reversing the direction of flow. The extracorporeal volume can be large and unsatisfactory for cardiovascularly unstable patients.

Selective affinity columns

Separated plasma passed through an affinity column allows selective removal of immunoglobulin (Ig) G (most pathogenic autoantibodies are IgG isotype) or specific autoantibody (using specific antigen as affinity ligand).[1] Staphylococcal A protein (an accident of nature which selectively binds IgG) columns can be reused about 20 times for a given patient, but are expensive.

Kinetics (Fig 3)

IgM is mainly intravascular and re-equilibrates slowly following plasma removal. Processing one plasma volume (3 litre for a 70 kg patient) removes 50% of IgM. Three consecutive daily treatments reduce IgM to 10–20% of pretreatment level. Smaller molecules (IgG or cytokines) re-equilibrate rapidly (50% of IgG is extravascular) so removal is less efficient. Typically, 40–60 mol of plasma/kg body weight are removed over 2–3 hours. Human albumin solution 4.5% diluted with normal saline is the routine replacement fluid. Three consecutive daily treatments also significantly reduce clotting factor concentrations. Plasmapheresis within days of diagnostic lung or renal biopsy risks bleeding into the biopsy. Cross-matched fresh frozen plasma (FFP) (10–15 ml/kg) should be included in the replacement fluid after each daily treatment.

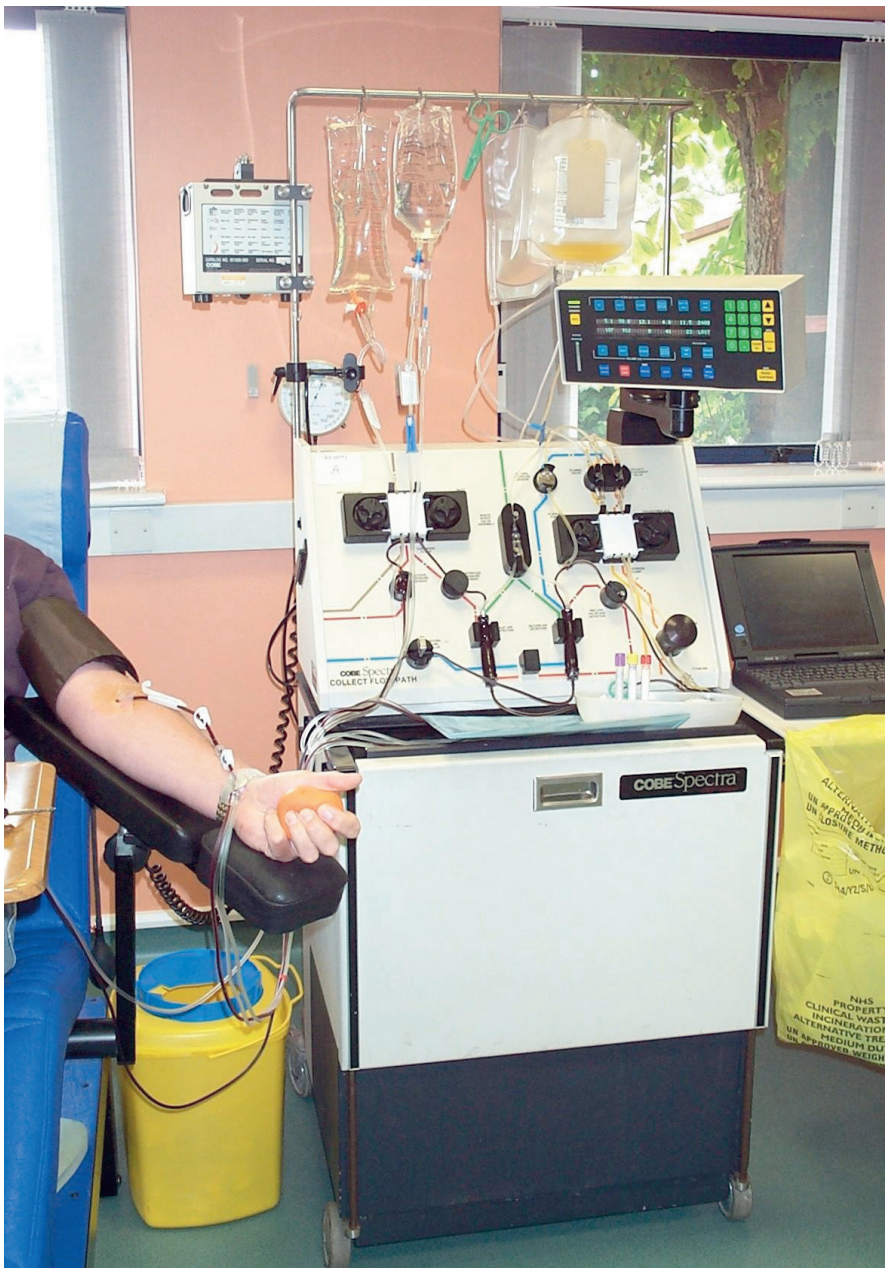

Fig 2. Continuous flow apheresis machine.

Complications

Fatalities are very rare and more likely to be related to the acute underlying condition (eg pulmonary haemorrhage in Goodpasture's syndrome). Other complications are:

- central line complications (pneumothorax, and internal bleeding)
- hypersensitivity reactions (most likely with FFP)
- infections (including prions) from blood products
- citrate anticoagulation; this is used almost universally and can lead to hypocalcaemia. FFP carries a high citrate load. Renal failure patients receiving large amounts of citrate may develop profound metabolic alkalosis.
- Loss of normal clotting factors increases haemorrhage risk, and loss of normal Ig (hypogammaglobulinaemia) increases infection risk.

Indications (Table 1)[2]

Plasmapheresis has applications in several areas of medicine:

- haematology
- renal diseases
- neurological diseases
- immunology
- metabolic disorders.

Haematology

Sickle-cell crisis – erythrophoresis

Erythrocyte exchange can help in the acute chest syndrome and other life-threatening crises, also for priapism or before surgery. The goal is to achieve sickle-cell concentrations below 30% with a haematocrit of not more than 120% of baseline.

Hyperviscosity due to blood cell excess

Hyperviscosity may present as a medical emergency with visual disturbance, cerebrovascular accidents or angina, but the commonest cause is polycythaemia. Venesection, rather than erythrophoresis, may suffice. Leukophoresis can help granulocyte excess (chronic myeloid leukaemia).

Monoclonal proteins and hyperviscosity syndromes

IgM paraproteins cause the most problems on a gram-for-gram basis. IgA and IgG3 paraproteins tend to aggregate and also contribute significantly to plasma viscosity. Symptoms can usually be alleviated long enough for myeloma chemotherapy to take effect with 2–3 daily treatments.

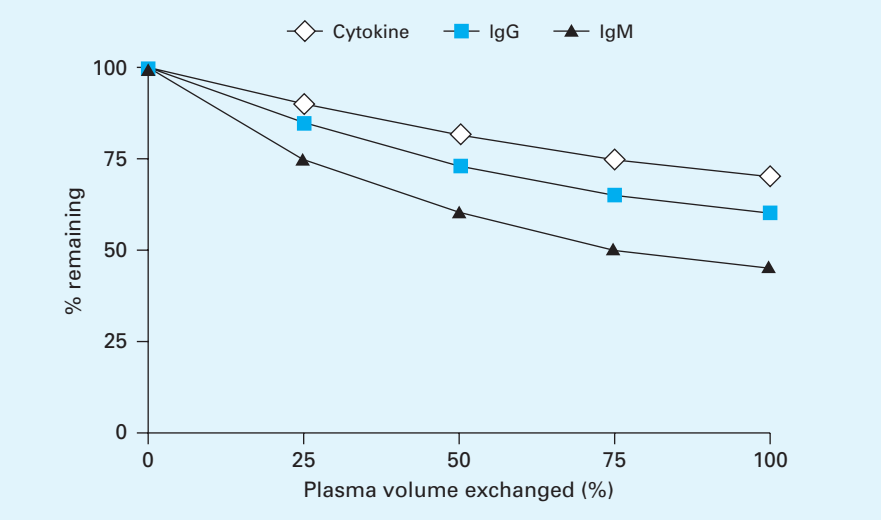

Fig 3. Kinetics for removal of immunoglobulin (Ig) M *v* IgG.

Thrombotic thrombocytopenia purpura

Abnormal von Willebrand factor (vWF) multimers develop, allowing platelet clumping and microvascular coagulation. Normally, a metalloprotease enzyme degrades multimers. This enzyme can be genetically defective or a blocking autoantibody may develop. Plasmapheresis can limit renal and/or neurological complications. FFP or cryosupernatant is preferred as replacement fluid and immunosuppression (corticosteroid therapy or other) is advised.[2–5] Plasma replaces VWF and enzyme and also removes autoantibody. Plasmapheresis with FFP replacement gives better outcomes than FFP infusion alone, reducing mortality from 85–15%.

Table 1. Indications for plasmapheresis.[2]

Evidence base	Disease	Refs	Factor removed
Accepted benefit	Cryoglobulinaemia		Cryoglobulin
	Hyperviscosity		Paraprotein
	TTP	3–6	Anti-metalloproteinase
	Goodpasture's disease	7,8	Anti-basement membrane
	Pauci-immune glomerulonephritis	7	ANCA? Other factors?
	FSGS	9,10	Permeability factor
	GBS	11	Anti-ganglioside?
	CIDP	12	?
	Myasthenia gravis		Anti-acetylcholine receptor
Possible benefit	Renal allograft rejection	13,14	Anti-ABO Anti-HLA
	Paraprotein-associated neuropathy	15,16	Paraprotein
	Multiple sclerosis	17	Cytokines
	Hyperlipidaemia	18	LDL
Doubtful value	SLE	19	Immune complexes
	Myeloma protein to prevent renal damage	20	Paraprotein

ANCA = antineutrophilic cytoplasmic antibody; CIDP = chronic inflammatory demyelinating polyneuropathy; FSGS = focal segmental glomerulosclerosis; GBS = Guillain–Barré syndrome; LDL = low-density lipoprotein; SLE = systemic lupus erythematosus; TTP = thrombotic thrombocytopenia purpura.

Renal diseases

Anti-glomerular basement membrane (GBM) antibody disease

Patients with pulmonary haemorrhage or advanced renal failure need urgent plasmapheresis. Concurrent immunosuppression with oral prednisolone 1 mg/kg, slowly reduced over six months, and cyclophosphamide 2–3 mg/kg/day is required.[6] A small pilot study in the mid-1980s pointed to added benefit when plasmapheresis is added to immunosuppression.[7] Daily plasmapheresis treatments, usually for 10–14 days, is required. Fluid overload may provoke haemorrhage. Patients treated before serum creatinine reaches 500 mmol/l do well,[6] but those who are dialysis dependent before treatment rarely become dialysis independent.

Antineutrophilic cytoplasmic antibody (ANCA)-associated glomerulonephritis

Wegener's granulomatosis and microscopic polyarteritis are both associated with ANCA. Opinion is divided whether the autoantibody ANCA is directly pathogenic in anti-GBM disease. Some studies have shown benefit when plasmapheresis is added to conventional immunosuppression.[6] With early treatment, some patients become dialysis independent.

Focal segmental glomerulosclerosis

Focal segmental glomerulosclerosis will recur in around 35% of renal transplants. Outcome is improved by starting plasmapheresis as soon as significant proteinuria is detected post-transplantation.[8,9] The pathogenesis is not understood, but a circulating permeability factor is suspected. Prednisolone reduces proteinuria in up to 40% of those with primary disease.

Renal transplants and plasmapheresis

Hyperacute rejection occurs in the operating room; it is an antibody-mediated rejection process due to either anti-ABO blood group antibodies or anti-HLA antibodies. In contrast, acute rejection occurs weeks to months post-transplantation, often in patients who were antibody cross-match negative pre-transplant but who develop allograft reaction post-transplant. Transplant biopsies showing IgG and complement C4d deposits suggest that humoral (antibody) rejection contributes to the process. Plasmapheresis combined with anti-T cell immunosuppression has been successfully used either pre-transplant (to prevent hyperacute rejection) or post-transplant to treat acute rejection.[10,11]

Neurological diseases

Guillain–Barré syndrome

Plasmapheresis became the gold standard, first-line treatment for Guillain–Barré syndrome (GBS) 15 years ago, with clear benefit proven by several well-designed clinical trials.[12] Therapeutic benefit is likely in cases treated within two weeks of developing symptoms. High-dose intravenous immunoglobulin (IVIG) is equally effective, logistically easier and with comparable costs. Few GBS patients now require plasmapheresis.[12] One-quarter of cases follow *Campylobacter jejuni* infection, a bacterium associated with the production of antiganglioside antibodies. Most cases benefit without immunosuppression. GBS may be a self-limiting, post-infectious process. There have been trials of affinity columns loaded with ganglioside.

Chronic inflammatory demyelinating polyneuropathy

Corticosteroids, IVIG and plasmapheresis are all effective in chronic inflammatory demyelinating polyneuropathy, suggesting an autoimmune type pathogenesis.[13] Relapse is common and, in contrast to GBS, parallel immunosuppression seems logical to prevent relapse. Plasmapheresis and IVIG seem equally effective, with benefit in around 80% of cases.[13]

Peripheral neuropathy associated with paraproteinaemia

Small, open trials showed partial benefit in some patients with peripheral neuropathy associated with paraproteinaemia when plasmapheresis removed IgG or IgA (but not IgM) paraproteins.[14] Predicting those who will benefit is difficult. It is not surprising that many cases fail to benefit as monoclonal gammopathy of uncertain significance is common, especially in the elderly (≤5%).

IgM paraproteins should not however be ignored. Neuronal deposits of IgM found in some cases on biopsy and IgM anti-myelin-associated glycoprotein in blood tests suggest a role in pathogenesis. The associated neuropathy is distal, demyelinating, sensory and often indolent. Logically, a course of plasmapheresis in this situation should be accompanied by concurrent cytotoxic therapy to switch off paraprotein production.[15]

Myasthenia gravis

Anti-acetylcholine receptor antibodies play a direct pathogenic role in myasthenia gravis and clinical recovery parallels titre reductions. Plasmapheresis helps patients who fail medical treatment and develop respiratory failure or swallowing difficulties. It is also used to prepare for thymectomy. There is no evidence to support long-term maintenance plasmapheresis. Anecdotally, plasmapheresis seems more effective than IVIG in this context.

Multiple sclerosis

Some patients (≤70% in open, uncontrolled small studies) with acute relapses unresponsive to steroids show clear benefit. Early intervention (within one month of relapse) seems necessary.[16] The factor or factors removed (query cytokines) remain elusive.

Immunology

Cryoglobulins

Plasmapheresis can be lifesaving in the exceptional cases where cryoglobulins are associated with a fulminant acute clinical picture. Technically, the procedure can be challenging, with cryoprecipitation and blockage in the tubing unless return fluids are adequately warmed. The cause of the cryoglobulinaemia must be determined and definitive therapy (eg cyclophosphamide for haematological malignancy) instituted. A case of type II cryoglobulinaemia associated with lymphoma is shown in Fig 4. Secondary complement C4 consumption was a useful indicator of relapse.

Other autoantibody-based disorders

Pemphigus vulgaris with erythroderma, the primary antiphospholipid syndrome (preventing recurrent miscarriage) and pregnancy complicated by anti-Ro/La (fetal heart block) are conditions for which anecdotal reports suggest that directly pathogenic antibody can be removed by plasmapheresis, with clinical benefit.

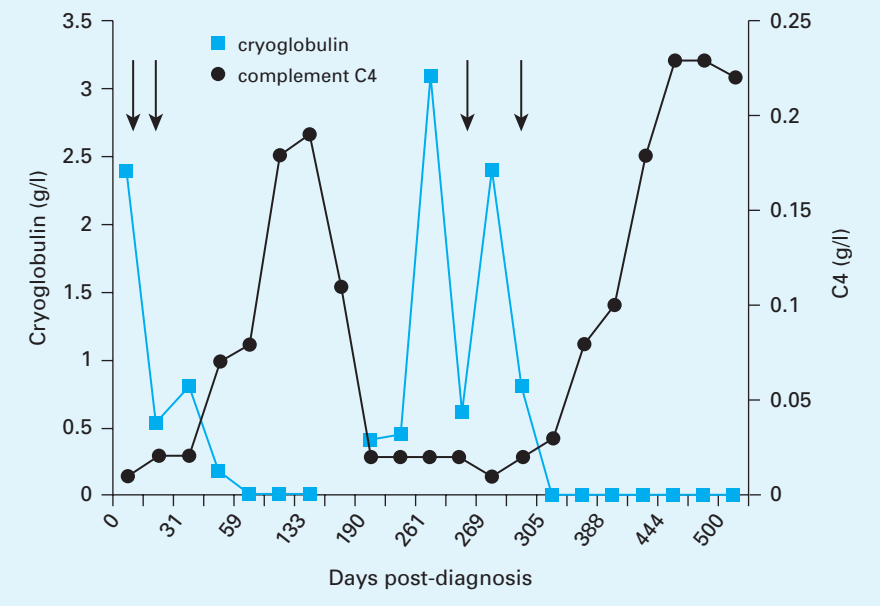

Fig 4. Treatment profile for a case of type II cryoglobulinaemia. Plasmapheresis rapidly reduced cryoglobulin levels (C4 consumption acted as an indirect measure of cryoglobulin). Cyclophosphamide was used to treat the underlying lymphoma.

Metabolic disorders

Homozygous familial hypercholesterolaemia may respond poorly to drugs and diet. Plasma exchange can remove the low-density lipoproteins. Dextran sulphate/cellulose affinity absorption columns are successfully used. Plasmapheresis has also been used in Refsum's disease, acute porphyria and thyrotoxic crises, with reported benefit.

References

1 Freedman J, Garvey MB. Immunoadsorption of factor VIII inhibitors. Review. *Curr Opin Hematol* 2004;11:327–33.

2 Smith JW, Weinstein R, for the AABB Hemapheresis Committee KL; AABB Hemapheresis Committee; American Society for Apheresis. Therapeutic apheresis: a summary of current indication categories endorsed by the AABB and the American Society for Apheresis. *Transfusion* 2003;43:820–2.

3 Cataland SR, Wu HM. Immunotherapy for thrombotic thrombocytopenic purpura. *Curr Opin Hematol* 2005;12:359–63.

4 Rock GA, Shumak KH, Buskard NA *et al.* Comparison of plasma exchange with plasma infusion in the treatment of thrombotic thrombocytopenic purpura. Canadian Apheresis Study Group. *N Engl J Med* 1991;325:393–7.

5 Coppo P, Bussel A, Charrier S *et al.* High-dose plasma infusion versus plasma exchange as early treatment of thrombotic thrombocytopenia purpura/hemolytic uremic syndrome. *Medicine (Baltimore)* 2003;82:27–38.

6 Winters JL, Pineda AA. New directions in plasma exchange. *Curr Opin Hematol* 2003;10:424–8.

7 Little MA, Pusey CD. Rapidly progressive glomerulonephritis: current and evolving treatment strategies. Review. *J Nephrol* 2004;17(Suppl 8):S10–9.

8 Johnson JP, Moore J Jr, Austin HA 3rd *et al.* Therapy of anti-glomerular basement membrane antibody disease: analysis of prognostic significance of clinical, pathologic, and treatment factors. *Medicine (Baltimore)* 1985;64:219–27.

9 Artero ML, Sharma R, Savin VJ, Vincenti F. Plasmapheresis reduces proteinuria and serum capacity to injure glomeruli in patients with recurrent focal glomerulosclerosis. *Am J Kidney Dis* 1994;23:574–81.

10 Pradhan M, Petro J, Palmer J, Meyers K, Baluarte HJ. Early use of plasmapheresis for recurrent post-transplant FSGS. *Pediatr Nephrol* 2003;18:934–8.

11 Hughes RA, Cornblath DR. Guillain-Barré syndrome. Review. *Lancet* 2005;366:1653–66.

12 Koller HK, Kieseier BC, Jander S, Hartung HP. Chronic inflammatory demyelinating polyneuropathy. Review. *N Engl J Med* 2005;352:1343–56.

13 Gloor JM, Lager DJ, Fidler ME *et al.* A comparison of splenectomy versus intensive posttransplant antidonor blood group antibody monitoring without splenectomy in ABO-incompatible kidney transplantation. *Transplantation* 2005;80:1572–7.

14 Ibernon M, Gil-Vernet S, Carrera M *et al.* Therapy with plasmapheresis and intravenous immunoglobulin for acute humoral rejection in kidney transplantation. *Transplantation Proc* 2005;37:3743–5.

15 Dyck PJ, Low PA, Windebank AJ *et al.* Plasma exchange in polyneuropathy associated with monoclonal gammopathy of undetermined significance. *N Engl J Med* 1991;325:1482–6.

16 Joint Task Force of EFNS and the PNS. European Federation of Neurological Societies/Peripheral Nerve Society Guideline on management of paraproteinemic demyelinating neuropathies. Report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society. *J Periph Nerv Syst* 2006;111:9–19.

17 Schilling S, Linker RA, Konig FB *et al.* Plasma exchange therapy for steroid-unresponsive multiple sclerosis relapses: clinical experience with 16 patients. *Nervenartz* 2006;77:430–8. [in German]

18 Thompson GR, Kitano Y. The role of low density lipoprotein apheresis in the treatment of familial hypercholesterolemia. Review. *Ther Apher* 1997;1:13–6.

19 Clark WF, Stewart AK, Rock GA *et al.* Plasma exchange when myeloma presents as acute renal failure: a randomized, controlled trial. *Ann Intern Med* 2005;143:777–84.

20 Lewis EJ, Hunsicker LG, Lan SP, Rohde RD, Lachin JM. A controlled trial of plasmapheresis in severe lupus nephritis. The Lupus Nephritis Collaborative Study Group. *N Engl J Med* 1992;326:1373–9.